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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,890	BRUSTLE, OLIVER	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6,8-12,15,46-48,50,76-83,85-94 and 96-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6,8-12,15,46-48,50,76-83,85-94 and 96-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendments filed September 14, 2005 and October 22, 2004 have been entered. The amendment filed February 14, 2005 has not been entered for reasons of record set forth in the Office communication of May 17, 2005. The remarks filed October 22, 2004 (hereinafter referred to as "the response") are considered herein. The remarks filed June 6, 2005 are also considered herein.

In the amendment filed October 22, 2004, Claims 2, 8, 47, 76, and 87 were amended. Claims 13, 84, and 95 were cancelled. Claims 100-104 were newly added.

Accordingly, Claims 2, 3, 6, 8-12, 15, 46-48, 50, 76-83, 85-94 and 96-104 are pending in the instant application.

The rejections of Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments to the claims and Applicant's arguments set forth at page 16 of the response and at pages 2-3 of the reply filed June 6, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 2, 3, 6, 8-12, 15, 46-48, 50, 76-83, 85-94 and 96-104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claims include new matter.

The claims have been amended so that they now recite that the cell composition comprises "about 100% isolated neural cells and neural precursor cells." However, the specification does not contemplate a cell composition comprising "about 100% isolated neural cells and neural precursor cells." Rather, the specification contemplates that the methodology presented permits the generation of **neural precursor cells** in a purity up to 100% (page 18, lines 30-32, emphasis added). Thus, the specification does not contemplate a cell composition that is made up of varying degrees and types of neural cells in combination with neural precursor cells. As amended, the claims now cover cell compositions that comprise a large percentage of mature, fully differentiated neural cells and a small percentage of neural precursor cells. However, the specification does not appear to contemplate cell compositions of this type as being part of the invention. The instant specification discloses, at page 24, lines 31-34, that immunofluorescent analysis of ES cell-derived neural spheres demonstrated that 66% of the cells were nestin-positive neural precursor cells. Although the instant specification states that the methodology described permits the production of neural precursor cell compositions with a purity far exceeding 85% and further that the methodology permits the generation of neural precursor cells in a purity up to 100% (page 18, lines 25-32), there is no demonstration of cell compositions exceeding 66% neural precursor cells. At page 9, paragraph 2 of the response, Applicants assert that support for this amendment is found in the specification at page 24, lines 31-38. However, this section describes the generation of a cell composition comprising 66% nestin-positive neural precursor cells, 34% βIII-tubulin-positive neurons, 30% GFAP-positive astrocytes, and 6.2% O4-positive oligodendroglial cells. Contrary to Applicant's assertion, the cited section provides support only for the specific cell composition described therein, and

not for the much broader claim language of a cell composition comprising "about 100% isolated neural cells and neural precursor cells."

Thus, the amended claims include new matter.

Enablement

Claims 2, 3, 6, 8-12, 15, 46-48, 50, 76-83, 85-94 and 96-99 stand rejected and Claims 100-104 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Actions of 2/26/03, 10/3/03, and 4/21/04, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 10 of the response, Applicant asserts that the phrase "about 100% isolated neural precursor cells" is enabled. At page 11, paragraph 1 of the response, Applicant asserts that the claims have now been amended to clarify that the claimed cell compositions comprise "about 100% isolated neural cells and neural precursor cells." Applicant further points to the specification at page 24, lines 31-38 for showing data that indicates the presence of neural antigens for neural precursor cells as well as neurons, astrocytes, and cells with oligodendroglial morphology. However, contrary to Applicant's assertion, the cited section does not describe a cell composition comprising "about 100% isolated neural cells and neural precursor cells." The cited section describes the generation of a cell composition comprising 66% nestin-positive neural precursor cells, 34% βIII-tubulin-positive neurons, 30% GFAP-positive astrocytes, and 6.2% O4-positive oligodendroglial cells. Thus, although the cell composition is described as comprising neural precursor cells, neurons, astrocytes, and cells with oligodendroglial morphology, there is nothing to suggest that these cell types make up 100% of the cells of the composition. It appears that the cell composition produced was not analyzed for the presence of other cell types.

At page 11, paragraph 2 of the response, Applicant asserts that the Declaration of Dr. Bruestle shows that the cell compositions of the present invention contain more than 99% neural cells (page 6, paragraph 17 of the Declaration filed 9/5/03). However, given that the specification does not describe or contemplate a cell composition comprising "about 100% isolated neural cells and neural precursor cells," for the reasons discussed hereinabove, the specification cannot broadly enable that which has not been described. As amended, the claims now cover a great variety of cell compositions, including cell compositions that comprise 100% neural precursor cells, or 99% neurons + 1% neural precursor cells, or 99% astrocytes + 1% neural precursor cells, or 99% oligodendrocytes + 1% neural precursor cells, or any other combination of neural cells. Thus, although the specification contemplates a cell composition comprising 100% neural precursor cells (see page 18, lines 30-32) and further describes a cell composition comprising 66% nestin-positive neural precursor cells, 34% βIII-tubulin-positive neurons, 30% GFAP-positive astrocytes, and 6.2% O4-positive oligodendroglial cells (at page 24, lines 31-38), it does not describe or enable what is now being claimed, namely a cell composition comprising "about 100% isolated neural cells and neural precursor cells."

At page 11, paragraph 3 of the response, Applicant points to Figure 5D of the specification and the accompanying description at page 12, lines 4-16, for showing cells differentiated from five-day old neural spheres and stating that "all cells depicted in this field express either of the two markers" referring to βIII-tubulin and nestin. However, a field of view under a microscope is not sufficient to describe an entire cell composition. There is nothing to suggest that the particular field of view shown in Figure 5D is representative of the entire cell composition.

At page 11, paragraph 4 of the response, Applicant concludes that because all cells expressed either nestin or βIII-tubulin, Applicant has demonstrated that the claimed cell composition comprises at or near 100% neural cells or neural precursor cells. Again, it is noted that there is nothing to suggest that the particular field of view shown in Figure 5D is representative of the entire cell composition. Moreover,

Applicant's arguments are not commensurate in scope with the scope of the claims, because a cell composition comprising βIII-tubulin-positive cells and nestin-positive cells (even if these were the only cells present in the culture) would not be considered enabling for the great variety of cell compositions covered by the claims.

At page 12, paragraph 5 of the response, Applicant asserts that the specification is enabling for the use of ES cells from species other than mice and humans because the specification points to prior art references that disclose embryonic stem cells from a variety of species, including rat, birds, fish, swine, cattle, and primates. However, the cited references do not pertain to the directed differentiation of ES cells from these species and the references cited in the rejection, including Bradley et al., Campbell and Wilmut, and Mullins et al., point to essential and significant differences between mouse ES cells and other ES-like cells reported in the art for other species, including the lack of germline transmission for species other than mice. Given the art-recognized differences, the skilled artisan would find it unpredictable whether protocols developed for the mouse would be appropriate for ES-like cells derived from other species, particularly non-mammalian species such as birds and fish.

At page 13, paragraphs 3-5, Applicant asserts that the enablement rejection relating to the genetic modification of human embryonic stem cells applies only to claims 13, 84, and 95, which specifically recite that the embryonic stem cells are genetically modified. Applicant further points out that these claims have been cancelled. Applicant further asserts that this rejection is limited to the genetic modification of **human** ES cells, not ES cells from other species. Applicant notes that the independent claims are not limited with respect to whether the embryonic stem cells are genetically modified, and therefore would cover the recited cell compositions, including cell compositions derived from embryonic stem cells whether or not the embryonic stem cells are genetically modified. In response, the Examiner agrees that the claims continue to encompass the use of genetically modified human embryonic stem cells. Thus, the rejection is maintained for reasons of record. The Examiner does not agree that the

rejection applies only to Claims 13, 84, and 95. It is noted that Claims 13, 84, and 95 depend from Claims 2, 76, and 87, respectively. Further, Applicant is reminded that the claims must be enabled over their full scope. As the claims continue to encompass the use of genetically modified human ES cells, the claims are rejected for lack of an enabling disclosure, for reasons of record.

Pharmaceutical Compositions

Claim 97 stands rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Action of 4/21/04, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 97 is directed to a pharmaceutical composition comprising the precursor cells of Claim 87. The precursor cells of Claim 87 are limited to cells that have the ability to differentiate into glial cells.

With regard to the rejection of Claims 46, 86, 97, and 99 for lack of an enabling disclosure for producing a therapeutic effect upon transplantation of the claimed cell compositions (i.e., the intended use of the claimed pharmaceutical compositions), Applicant asserts that Example 4 provides a therapeutic use for transplanting oligodendroglial/astrocytic precursors into myelin-deficient rats for the purpose of myelin regeneration. However, there is nothing in Example 4 that points to a therapeutic outcome and Applicant provides no support for the assertion that Example 4 provides a therapeutic use. Although donor mouse cells were detected in the rat brain following embryonic transplantation, no therapeutic effect was demonstrated.

The rejection of Claims 46, 86, and 99 under 35 U.S.C. 112, first paragraph, for failing to provide an enabling disclosure for a pharmaceutical use of the claimed invention, is withdrawn in view of Applicant's arguments relating to Example 5.2, as set forth at pages 14-16 of the response. The Examiner acknowledges that transplantation of mouse ES cell-derived neural cell compositions into adult rat brain

with ibotenic acid-induced striatal lesions resulted in reduced amphetamine-induced rotational behavior. However, Claims 46, 86, and 99 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 2, 3, 6, 8-12, 15, 46-48, 50, 76-83, 85-94 and 96-104 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,980,885 (Weiss et al., 1999; filed June 7, 1995).

The claims have been amended so that they are now directed to cell compositions comprising "about 100% isolated neural cells and neural precursor cells." As such, the claims cover heterogeneous cell compositions comprising neural precursor cells and other types of neural cells.

The instant claims are product-by-process claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a

product does not depend on its method of production. See M.P.E.P. 2113. Thus, the claims read on neural stem cells disclosed in the prior art, for the reasons set forth herein below.

Weiss et al. (1999) disclose mammalian neural stem cells. These cells can be derived from embryonic, juvenile, or adult mammalian neural tissue. The cells can be induced to differentiate into neurons, astrocytes, and oligodendrocytes. Although the instantly claimed cells are limited to cells derived from embryonic stem cells, no particular identifying characteristics are recited in the claims other than the requirement that the cells differentiate into "neuronal cells or glial cells" or just "glial cells." The cells disclosed by Weiss et al. satisfy this limitation. Weiss et al. further disclose that the neural stem cells form neurospheres in suspension culture (Columns 33-34). The specification particularly states that "[i]n the continued presence of a proliferation-inducing growth factor such as EGF or the like, precursor cells within the neurosphere continue to divide resulting in an increase in the size of the neurosphere and the number of undifferentiatated cells." Example 6, *inter alia*, provides a disclosed embodiment of a cell composition comprising 100% neural cells and neural precursor cells, as instantly claimed. The example discloses that neurospheres were dissociated and single cells from the dissociated neurospheres were suspended in tissue culture flasks. A percentage of dissociated cells began to proliferate and formed new neurospheres largely composed of undifferentiated cells. Thus, both the starting material (i.e., the single cell suspension) and the final culture of Example 6 represent cell compositions as claimed. The reference further discloses that the neural stem cells are non-tumorigenic (Column 1, lines 39-44) and can be used for autologous transplantation (Column 1, lines 49-50).

In the absence of evidence to the contrary, the neural stem cell compositions disclosed by Weiss et al. are indistinct from the cell compositions instantly claimed.

Thus, the claimed compositions are disclosed in the prior art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER